REMARKS

I. Status of the Claims

Claims 1-3, 9, 11-12, 17, 19-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-83 are pending.

II. Response to the Rejections under 35 U.S.C. § 112 First Paragraph Enablement Requirement

1. Enablement of Solvates

Claims 1-3, 9, 11-12, 17, 19-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-83 were rejected under the enablement requirement of 35 U.S.C. § 112 first paragraph. The applicants respectfully traverse the rejection.

The Examiner appears to have dropped the contention that *Solid State Chemistry and its Applications* by A.R. West ("West") states demonstrates lack of enablement by demonstrating solvate formation is unpredictable, but now instead contends that Vippagunta establishes lack of enablement by demonstrating solvate formation is unpredictable. Specifically, it is contended that

> [Vippagunta] teaches that making solvates from organic compounds is not "merely routine" and is very unpredictable: "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules m the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates."

MPEP 707.07(f) states that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."

The Office Action has not taken full account of the arguments presented previously by the applicants, contrary to the Examiner's obligation to do so, and the Examiner continues to err by predicating his conclusion that the claims lack enablement on a **single factor** – the supposed lack of predictability of solvate formation – whilst ignoring the overwhelming evidence that the applicants presented of the highly routine methods available for preparing, screening, and evaluating solvates and hydrates. While the same factor of unpredictability existed in *Wands* (and, it might be noted to a much higher degree than it can be considered to be present here), the court in *Wands* nevertheless found that the availability of routine screening methods and high level of skill in the art resulted in the claims being enabled *as a matter of law*. This was despite the much more complicated technology at issue in *Wands* as compared to the present application. The Office has continued to focus on the single issue of the supposed unpredictability whilst completely failing to consider and address the overwhelming evidence of the straightforward technology and routine techniques available for forming, screening, and evaluating solvates and hydrates provided by the applicants.

The Examiner is respectfully reminded that **an application is *presumed* to comply with the first paragraph of 35 U.S.C. § 112**, unless there is a reason to doubt the objective truth of the specification. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). The burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the Office. *Id.* "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning *which is inconsistent with* the contested statement." MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971))(emphasis added).

An application satisfies the enablement requirement if the disclosure has sufficient information to enable the person skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. *Id* at 737. The fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. on other grounds sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976).

The **Office has not provided reasoning which is *inconsistent with* the enablement of the rejected claims**, as the Office is required under MPEP 2164.01 to present in order to support an enablement rejection.

It appears from the reasons given for the rejection that the Examiner contends that formation of crystalline solvates is unpredictable, particularly with regard to the number of molecules of water or solvent incorporated into the crystal lattice, whether the crystal forms are more or less stable in the presence of water and/or solvents, and whether the crystal structures of the hydrates and solvates can be predicted by computer.

The applicants respectfully point out that absolute predictability is not required in order to satisfy the enablement requirement.

Further, the passages from Vippagunta relied upon in the Office Action, which focus on the lack of predictability of the *structure* of solvates, have little relevance to the issue enablement of the claims at issue here because the claims do not require solvates of a particular structure. The claims do not recite solvates having a particular number of solvent atoms, or a particular

structural lattice, or whether the solvates are stable which seem to be the issues addressed by Vippagunta which concern the Examiner. The applicants' claims, in fact, do not recite any particular features of hydrates and solvates that they encompass. Rather, the claims include all forms of the compounds defined in claim 1, including any hydrate or solvate.

Vippagunta suggests that many organic compounds are capable of forming solvates. Vippagunta indicates that "most organic ... compounds of pharmaceutical relevance can exist in one or more to unique crystalline forms" and that solvates are among the "common crystalline forms found for a given drug substance" (p. 4 col. 1) and that "[i]t has been "estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates" (p. 15 col 1). Thus, it does not seem to the applicants that Vippagunta supports the Examiner's contention that it would be particularly unpredictable whether solvates of compounds of the invention could be formed.

Even if solvate formation were somewhat unpredictable, as the Examiner contends, the claims would still satisfy the enablement requirement because such experimentation as might be required to prepare salts or hydrates of the compounds of the invention would be routine and well within the capacity of the skilled artisan, and would therefore not be undue, as is demonstrated by the references the applicants have cited previously.

The applicants provided evidence that making hydrates and solvates is easy, simple, requires few steps, and demands little time, and that the person of skill in the art routinely engages in such experimentation, and that the techniques for performing such experimentation are well known.

To make hydrates and solvates, samples of the organic compound are simply exposed to water or various different solvents. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from water or solvent. In fact, it is difficult to conceive of a scientific method that is simpler to perform than

placing a powder on a dish and letting it sit out on a humid day. Other typical procedures for making and identifying hydrates and solvates are described on pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999.

Once solvates are formed, they can be readily analyzed by routine methods. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light microscopy, and hot stage microscopy or other routine techniques to detect and quantify the presence of solvate molecules in the sample. See p. 18, col 2 of Vippagunta.

To screen the various solvents and conditions that might be used to form solvates merely uses methods that are very well known in the art and considered quite simple. As the applicants have pointed out previously, the process is *so* routine as to be amenable to high throughput screening, for example high throughput crystallization as described, for example, in Morisette, *et al.*, *Adv. Drug Delivery Rev.*, **2004**, *56*, 275-300.

A proper analysis of the issue of enablement under *Wands* must take proper account of <u>all</u> the factors relevant to the issue of enablement. The Office continues to attempt to base its enablement rejection solely on the alleged unpredictability of solvate formation and the fact that no specific examples of solvates have been described in the specification. Importantly, however, *Wands* establishes that unpredictability (which was the main grounds of improper enablement rejection in *Wands*), even if it were established, is not dispositive. Similarly, there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). Given that one skilled in the art could make and identify various hydrates and solvates of a particular organic molecule using the routine screening methods discussed above, no working example is necessary to enable the invention.

Wands, in fact, mandated that numerous factors be considered in evaluating enablement rather than the narrow approach taken by the Office here.

Any unpredictability or the absence of examples of solvates specifically described as solvates or hydrates should be found to be **clearly outweighed by the other factors** considered in *Wands*.

As to the **nature of the invention**, the claims are directed to pharmaceutical compounds and salts thereof. It is well known that stable, crystalline solvates and hydrates can be formed from such compounds (even though the claims do not require the solvates and hydrates to be crystalline or stable).

As to **state of the prior art,** and **predictability in the art**, the Office argues that whether a hydrate or solvate will be formed in a given case, and its exact structure, cannot be reliably predicted *a priori*. Although the Office focuses on this supposed unpredictability, the Office acknowledges that the prior art shows that a high percentage of pharmaceutically active compounds are found to be capable of forming crystalline solvates. Thus, it must be acknowledged that even if predicting whether a given solvate is unpredictable, formation of solvates generally is not at all unusual, and can be performed using routine and predictable methods. The Office does not acknowledge the well-established and routine methods established in the art for preparing, screening, and evaluating solvates and hydrates.

As to the **amount of direction**, and the presence or absence of **working examples**, the applicants respectfully point out the absence of specific direction or working examples is not required when the techniques required to practice the invention are entirely routine and well known. As to the aspect of the invention at issue here (formation of solvates and hydrates), the techniques for preparing, screening, and evaluating solvates and hydrates are well known and routine, and nothing would be gained by describing such methods in the specification. "A patent need not teach, and preferably omits, what is well known in the art." *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991).

Although the Office recognizes that he **level of skill in the art** is high, the does not accord sufficient weight to this factor. The person skilled in the art who would prepare solvates or hydrates of the compounds of the invention would typically be a highly skilled artisan, such as a Ph.D. qualified scientist, in the art of chemistry or pharmaceutical formulation. The person skilled in the art would be familiar with the routine techniques available for preparing, screening, and evaluating solvates and hydrates. The person skilled in the art would be capable, if necessary, of routinely screening many different compounds of the formulae defined in the claims, using a variety of solvents, and conditions for solvate or hydrate formation, and would have routine methods for evaluating the results of such screening.

Based on the foregoing it is clearly that the **quantity of experimentation** needed to practice the invention would clearly not be undue. Insofar as there might be unpredictability in solvate formation, the art has responded by providing routine, high throughput methods for preparing, screening, and evaluating solvates and hydrates. *Wands* has acknowledged that routine screening does not constitute undue experimentation.

As the applicants noted previously, even a cursory search of the U.S.P.T.O. database of issued patents suggests a substantial number of pharmaceutical patents with claims referencing solvates and hydrates , yet having no enablement rejections to the same: see, e.g., Patents. Nos. 7232823, 7230024, 7230002, 7229991, 7227027, 7211591, 7173037, 7157466, and 7105523. The Office has not explained the difference between these patents and the present application with respect to enablement of hydrates and solvates.

Since the preparation of solvates is the type of experimentation that is routinely engaged in the art, and merely involves the use of well known methods without excessive effort, applicants respectfully request that the rejection of claims 1-3, 9, 11-12, 17, 19-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-83 under the enablement requirement of 35 U.S.C. § 112 first paragraph based upon the recitation of solvates be withdrawn.

2. Enablement of Methods of Modulating a $5HT_{2C}$ receptor

Claims 33-34 were rejected under the enablement requirement of 35 U.S.C. § 112 first paragraph. Applicants respectfully traverse the rejection.

As explained above, applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112, and the burden of establishing a basis reason to doubt the objective truth of the specification rests upon the examiner. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)).

The applicants noted previously that **the Office Action did not give any reasons why claims 33-34 were rejected**. The reasons given for the rejection of 33 and 34 (along with other claims) appeared to state that the Examiner contended that treatment of $5HT_{2C}$-mediated *disorders* was not reasonably enabled by the specification. The applicants pointed out previously that even if this were true, the reasons would not support the rejections of claims 33 and 34 which are directed to modulating $5HT_{2C}$ *receptor* response.

The applicants are concerned that the Office Action completely failed to address the applicants' response with regard to these claims. MPEP 707.07(f) states that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it." However, the Examiner does not appear to have taken any account at all of applicants' remarks with regard to claims 33 and 34.

The applicants pointed out previously that the skilled artisan could readily modulate $5HT_{2C}$ receptor response using the compounds identified in the specification because to do so

merely requires contacting the receptor with the compound. On p.1 line 5 of the specification it is stated the compounds of the invention are modulators of the $5HT_{2C}$ receptor. A method for modulating the $5HT_{2C}$ receptor, and data for representative compounds are provided in Example 1. The Office has not provided any reasons to doubt the objective truth of the statements and thus has provided no basis for the rejection.

Applicants respectfully request reconsideration of the rejection of claims 33-34 under the enablement requirement of 35 U.S.C. § 112 first paragraph, and respectfully submit that upon such reconsideration the rejection should be withdrawn.

3. Enablement of Methods of Treatment

Claims 35-37, 39, 45-46, 48-49, 51-52, 54 and 80-83 were rejected under the enablement requirement of 35 U.S.C. § 112 first paragraph. The applicants respectfully traverse the rejection. The applicants again regretfully note that the Examiner again does not appear to have taken full account of the applicants' arguments and the evidence already presented by the applicants in response to the same rejection made previously.

The Office Action alleges that the specification is not adequately enabled to treat $5HT_{2C}$-receptor mediated disorders. **No evidence is presented to support the rejection**, since the Office appears now to have dropped its arguments suggesting that Cryan, *et al.*, *Hum. Psychopharmacol. Clin. Exp.*, **2000**, *15*, 113-135 ("Cryan 1"), supports the rejection by showing "the speculative nature of the role of 5-HT receptors with the treatment of depression" in view of applicants' showing that another paper by Cryan indicated that "the results strongly implicate a role for 5-HT_{2C} receptors in the behavioral effects of antidepressant drugs".

The Examiner is again respectfully reminded that **an application is *presumed* to comply with the first paragraph of 35 U.S.C. § 112**, unless there is a reason to doubt the objective truth of the specification. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). The burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the Office. *Id.* It is incumbent upon the Patent Office, whenever a rejection

on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning *which is inconsistent with* the contested statement." MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971))(emphasis added).

An application satisfies the enablement requirement if the disclosure has sufficient information to enable the person skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. *Id* at 737. The fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. on other grounds sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976).

The Office has again provided no reasoning which is *inconsistent with* the enablement of the rejected claims, as the Office is required to present in order to support an enablement rejection.

The entirety of the reasoning given to support maintaining the rejection is set forth in the Office Actionas follows:

> Applicant argues by citing page numbers from the specification that it is Applicant's position that the instant compounds are capable of treating the various stated disorders identified in the rejected claims. However, Applicant admits that "further experimentation such as obtaining clinical data might be required before a given compound would be able to be sold as a drug for the treatment of any particular disease" clearly shows an acknowledgement on the part of the

Applicant that the enablement requirement has not been met. As such. Examiner maintains this rejection.

In addition to mischaracterizing the applicants' arguments, the Office's response to applicants' arguments is insufficient to support maintaining the rejection.

The Examiner's dismissal of the applicants' citation to the specification as supporting applicants' arguments that the claims are adequately enabled is not an appropriate response to the rejection. It is a role of the specification to teach the person skilled in the art how to make and use the invention. 35 U.S.C. § 112. Further, as has been pointed out above, the law requires the statements in the specification to be accepted as true unless the Office provides evidence or reasoning to the contrary.

Since the Office Action has provided no evidence to controvert them, the statements in the specification supporting enablement must be accepted as true. As the applicants pointed out previously, the specification states: on p.3 line 33 that a "$5HT_{2C}$ agonist can be an effective and safe anti-obesity agent"; on p. 4 line 3-7 that $5HT_{2C}$ agonists are useful as anti-panic agents, are useful for treating sexual dysfunction, psychiatric symptoms, and eating disorders; on p.6 line 14 that $5HT_{2C}$ agonists are useful for treating Alzheimer's disease. It is also stated that the compounds are useful for the various diseases in the specification on p. 43-47. These statements provide the requisite presumptive enablement. The statements in the specification have not been controverted by evidence, are legally presumed to be true, and are therefore sufficient to enable the claims.

The Office's response to the applicants' arguments is also incomplete because it fails to take account of (and, in fact, entirely ignores) the additional **evidence** in the form of references supporting enablement of the claims which was provided by the applicants. The applicants pointed out that Cryan 1 (the only reference cited by the examiner as supposedly showing lack of enablement) concluded that the $5\text{-}HT_{2C}$ receptor plays an important role in antidepressant responses, stating that it appears to play "a definite role ... in mediating the antidepressant

response" (see Cryan 1, p. 124). The applicants provided the examiner with a further reference by Cryan, *et al.*, *J. Pharmacol. Exp. Ther.*, **2000**, *295*, 1120-26 ("Cryan 2") which demonstrated that 5-HT_{2C} receptor selective agonists were active in animal models of depression, that the effects of antidepressants were blocked by 5-HT_{2C} receptor selective agonists. The authors indicated that "the results strongly implicate a role for 5-HT_{2C} receptors in the behavioral effects of antidepressant drugs" and were "evidence that the 5-HT_{2C} receptor may indeed be a novel target for the development of antidepressants and perhaps of drugs effective in other psychiatric disorders involving 5-HT". The applicants also provided the Examiner following four additional references, representing only a sampling of the abundant literature on the subject, demonstrate the validity of $5HT_{2C}$ receptor as a target for a variety of different CNS disorders: Wood *et al.*, *Drug Dev. Res.*, **2001**, 54, 88; Bos *et al.*, *J. Med. Chem.*, **1997**, *40*, 2762; Martin, *et al.*, *J. Pharmacol. Exp. Ther.*, **1998**, *286*, 913; and Grottick, *et al.*, *J. Pharmacol. Exp. Ther*, **2000**, *295*, 1183.

Insofar as the Office Action does respond to applicants' arguments on the issue of enablement of the rejected method of treatment claims, the applicants' arguments on the issue of enablement have been mischaracterized. The Examiner asserts that the applicant has "clearly" acknowledged that "the enablement requirement has not been met" merely because applicants stated that "further experimentation such as obtaining clinical data *might be* required before a given compound would be able to be sold as a drug for the treatment of any particular disease" (emphasis added). That assertion is unwarranted. The Examiner could not reasonably have read the applicant's traversal of the enablement rejection (which extended over six pages of applicants' prior response) as a "clear acknowledgement" that the rejection was correct.

The applicants are concerned, moreover, that the Examiner's suggestion that if the applicants had acknowledged the *possibility* that *some* further experimentation *might* be required before applicants' invention was ready for commercialization that this would be inconsistent with the enablement requirement being fulfilled reflects a serious misunderstanding on the Examiner's part of the requirements for making a proper enablement rejection. MPEP 2164, *et seq*, sets

forth these requirements. The MPEP clearly points out that "[t]he test of enablement is *not* whether *any* experimentation is necessary, but whether, if experimentation is necessary, it is undue." MPEP 2164.01 (quoting *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976)) (emphasis added). If the applicants had acknowledged any need for further experimentation, such an acknowledgement could not, according to the MPEP, be considered a "clear acknowledgment" that "the enablement requirement has not been met".

The applicants' remarks in response to the previous rejection adequately demonstrated that such experimentation as might be required to put the applicants' invention into practice in a commercial context would certainly not be undue. As the applicants pointed out previously, the courts have *expressly recognized* that the level of validation required for patentability is *much lower* than required, for example, to obtain F.D.A. approval to market a new drug. *See, e.g., In re Brana*, 51 F.3d, 1560, 1568 (Fed. Cir. 1995) ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development."). In view of the complexity of developing the field of developing new pharmaceuticals, the quantity of experimentation required to practice the invention of the rejected claims cannot be described as undue. *Wands* recognized that the need for further experimentation is not inconsistent with enablement: "the key word is undue not experimentation". *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (quoting *In re Angstadt*, 537 F.2d 498, 504, 190 (C.C.P.A. 1976) (internal quotation marks omitted). Pharmaceutical drug discovery and development, is complex, to be sure, but the law does not preclude inventions in complex fields from patent protection. It is recognized that the fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983)). Few fields of endeavor rival the complexity of developing pharmaceuticals. Drug companies "typically engage in" a substantial amount of experimentation in the course of drug development. The amount of experimentation that would be required to practice the claimed invention commercially would certainly not be "undue".

A proper analysis of the issue of enablement under *Wands* must take proper account of all the factors relevant to the issue of enablement. The applicants respectfully submit that a proper consideration of the relevant *Wands* factors should lead the Office to conclude that the rejected method of treatment claims are adequately enabled.

As to the **nature of the invention**, the claims are directed methods for treating $5HT_{2C}$-mediated diseases by administering compounds according to Formula I, which have been shown to modulate the $5HT_{2C}$ receptor as agonists. The nature of the invention, therefore, is that the rejected claims are directed to the use of the specified compounds as pharmaceuticals. Companies developing new pharmaceuticals typically engage in a relatively large amount of complicated experimentation.

As to **state of the prior art,** and **predictability in the art**, the applicants have provided ample references showing that the $5HT_{2C}$ is a well-validated pharmacological target with regard to the diseases to the treatment of which the rejected claims are directed.

As the examiner conceded previously, the **level of skill in the art** is extremely high. The persons skilled in the art will typically be Ph.D. scientists specializing in drug discovery and development and/or medical doctors specializing in treatment of the diseases that are the subject of the claims. Those persons will be capable of designing and performing highly sophisticated experiments.

The applicants have provided considerable **guidance and working examples** for carrying out the invention, including detailed information defining the compounds of the invention as well as defining preferred embodiments of the compounds and describing methods of making the embodiments (see pages 15-43, 61-63 and 67-97); guidance regarding the formulation and administration of the compounds (pages 52-61); and extensive guidance as to the methods of treatment is provided (see pages 43-52), including identifying numerous $5HT_{2C}$ receptor-mediated diseases (see pages 43-45). Screening methods are also provided (pages 65-

67), as well as data for representative compounds demonstrating in vivo activity in an animal model relevant to treatment of obesity.

The **amount of experimentation** that would be required to practice the claimed invention would therefore not be "undue".

In view of the foregoing, reconsideration of the examiner's findings concerning enablement of claims 35-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-83 is respectfully requested. It is respectfully submitted that upon such reconsideration, the examiner should conclude that the rejection for lack of enablement under 35 U.S.C. § 112 should be withdrawn.

IV. Response to the Rejections under 35 U.S.C. § 103(a)

1. Rejection of Claims 1-2, 11-12, 17, 19-26, 32 and 79 over Allen, U.S. Patent No. 3,751,417

Claims 1-2, 11-12, 17, 19-26, and 79 were rejected under 35 U.S.C. 103(a) as allegedly obvious over Allen, U.S. Patent No. 3,751,417 (the "'417 patent"). The applicants respectfully traverse the rejection.

The applicants note, with appreciation, that the Examiner has withdrawn the rejection of claim 32, agreeing with the applicants that the '417 patent does not suggest making pharmaceutical compositions of the compounds according to the rejected claims.

The applicants respectfully submit, however, that the '417 patent also would not have rendered the compounds of the rejected claims obvious to the person skilled in the art.

The prior Office Action stated that "claim 1 of the reference renders the scope of instant claim 1 obvious" and that, "for example ... 2-methyl-1-(4-methylphenyl)-piperazine [and] 1-(4-methoxyphenyl)-2-methyl-piperazine" which were said to be disclosed in the reference, rendered the claims obvious. It was maintained that the presently claimed compounds would have been obvious because "one skilled in the art would have been motivated to prepare compounds as

taught in the reference with the expectation of obtaining compounds falling within the generic teaching of claim 1."

In response, the applicants' pointed out that while the reasons given for the rejection depended heavily on the fact that 2-methyl-1-(4-methylphenyl)-piperazine and 1-(4-methoxyphenyl)-2-methyl-piperazine supposedly were disclosed in the reference and fell within the scope of the claims, both these compounds were, in fact, expressly excluded from the scope of claim 1 (and therefore from the scope of all the dependent claims).

The most recent Office Action "disagrees" with the applicants' statement that 2-methyl-1-(4-methylphenyl)-piperazine is excluded from the scope of claim 1, and states that "claim 79 exactly teaches this compound."

The Office Action, however, is simply **incorrect** in asserting that claim 1 does not exclude 2-methyl-1-(4-methylphenyl)-piperazine. 2-Methyl-1-(4-methylphenyl)-piperazine is listed in the proviso excluding certain compounds from the scope of claim 1, which reads, in relevant part: "provided that the compound is not ... 2-Methyl-1-p-tolyl-piperazine." The applicants respectfully point out that the term "p-tolyl" refers a "4-methylphenyl" group, as evidenced by the definition from the *Shorter Oxford English Dictionary* (Oxford University Press, 6th Edition, 2007) reproduced below (the p-, an abbreviation for "para", referring to the methyl substituent being in the 4-position of the phenyl ring):

tolyl /'tɒlʌɪl, -lɪl/ *noun.* M19.
[ORIGIN from TOL(UENE + -YL.]
CHEMISTRY. Each of three isomeric cyclic radicals, $CH_3C_6H_4$·, derived from toluene. Formerly also = **BENZYL.**

Lest there be any doubt, the applicants expressly provided the structure of 2-methyl-1-p-tolyl-piperazine, the compound expressly excluded from the scope of claim 1 and all its dependent claims, in Table 3 on p. 43 of the specification. The compound in the third row of Table 3 on p. 43, identified as 2-methyl-1-p-tolyl-piperazine, the compound *expressly excluded*

from claim 1, has **exactly the same structure** as the compound (2-methyl-1-(4-methylphenyl)-piperazine) which the Office Action contends is *not excluded* from claim 1.

The relevance of the Office Action's statement as to what claim 79 "teaches" is not understood. However, it may suffice to point out that claim 79 also does not encompass 2-methyl-1-(4-methylphenyl)-piperazine because it depends from, and therefore incorporates all of the limitations of claim 1, including the exclusion of 2-methyl-1-(4-methylphenyl)-piperazine. It might also be pointed out that claim makes no mention of 2-methyl-1-(4-methylphenyl)-piperazine, but rather reads as follows:

> 79. The compound according to claim 1 wherein:
> R_1 is H, methyl, ethyl, *n*-propyl, *iso*-propyl or *n*-butyl;
> R_2 is a vinyl, methyl, ethyl, *n*-propyl, C_{1-4} haloalkyl or $-CF_3$;
> R_3 is H or F;
> R_4 is selected from the group consisting of H, cyano, F, Cl and Br;
> R_5 is selected from the group consisting of H, CH_3, $CH(CH_3)_2$, OCF_3, CF_3, F, Cl and Br;
> R_6 is selected from the group consisting of H, F, Cl and Br; and
> R_7 is selected from the group consisting of H, CH_3, F, Cl and Br

Claim 79 does not encompass 2-methyl-1-(4-methylphenyl)-piperazine because claim 79 depends from claim 1, and therefore incorporates all of the limitations of claim 1, including the exclusion of 2-methyl-1-(4-methylphenyl)-piperazine.

With regard to 1-(4-methoxyphenyl)-2-methyl-piperazine, the Office concedes that the claims exclude this compound but states that:

> "[h]owever, the proviso does not exclude the ethyl or ethoxy versions of this exemplified compound, or positional isomers. As such, Examiner maintains this rejection with regards to claims 1-2, 11-12, 17, 19-26, and 79 ... it would have been obvious to one having ordinary skill in the art at the time that .the invention was made to make similar compounds of Allen, et al."

The Office Action fails to give legally adequate reasons for maintaining the rejection.

Apart from incorrectly stating that claim 1 does not exclude 2-methyl-1-(4-methylphenyl)-piperazine (which is, in fact excluded from claim 1), the sole reasoning given for maintaining the rejection is that claim 1 does not exclude "ethyl or ethoxy versions" of 1-(4-methoxyphenyl)-2-methyl-piperazine. The Office also implies that the '417 patent describes compounds that are somehow "similar" to the compounds of the claims.

As the applicants pointed previously, the Supreme Court has recently clarified that for an invention to be obvious under § 103, the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) must be considered, including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007). An *explicit rationale* for why one having ordinary skill in the art would have modified the prior art in the manner claimed must be set forth. *Id.* at 1741.

Recent case law has made it clear that "it remains necessary to identify some reason that would have led a chemist to modify a known compound *in a particular manner* to establish *prima facie* obviousness" reaffirming that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention' was also required." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)) (emphasis added).

The Office Action, however, completely fails to meet the requirement of providing any reason that the person skilled in the art would have modified any known compound in the '417 patent and modifying it in the particular manner that would be required to produce compounds within the scope of the rejected claims.

In *Takeda*, the Federal Circuit upheld a lower court finding that a claim to an ethyl-substituted compound was not rendered obvious by a prior art disclosure of a corresponding methyl-substituted compound, in part because there was reason apparent to select the prior art methyl compound as a lead compound to modify to arrive at the claimed invention. *Takeda*, 492 F.3d at 1358.

Contrary to the legally correct approach mandated by the Supreme Court in *KSR* and followed by the Federal Circuit in *Takeda*, the Office fails to provide any reasoning that it would have been obvious to the person skilled in the art to modify compounds disclosed in Allen to provide compounds of the invention. The Office has not identified any reason it would have been obvious the person skilled in the art would choose the particular compounds pointed to in the Office Action (2-methyl-1-(4-methylphenyl)-piperazine or 1-(4-methoxyphenyl)-2-methyl-piperazine) for further modification, nor why it would have been obvious for the person skilled in the art, having selected those compounds, to modify them in the "particular manner" make compounds within the scope of the rejected claims. Thus, the Office has not identified "some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness" as is necessary under *Takeda*.

The applicants respectfully submit that it would not, in fact, have been obvious for the person skilled in the art to the appropriate compounds from the '417 patent and modify them in the particular manner that would be required to provide compounds within the scope of the rejected claims.

First, as the applicants pointed out previously (although the point was not addressed by the Office in its reconsideration of the rejection), the '417 patent is not analogous art relative to the present invention. In order to be relied upon to support a rejection under 35 U.S.C. §103(a), a reference must be analogous art, meaning that it is a reference which "because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his or her invention as a whole." MPEP 2141.01(a). The applicant's invention

relates to the development of compounds for the modulation of $5HT_{2C}$ receptors while the '417 patent relates to a completely different problem, namely the treatment of pain. .

Second, the compounds which the Examiner appears to consider would have been obvious to modify to provide compounds according to the invention are ones having not disclosed as having any biological activity whatsoever. The Office Action does not explain, however, how the reference's discussion of these (so far as the prior art is concerned) inactive compounds "would have commended itself" to the inventors' attention in considering their novel $5HT_{2C}$ receptor modulators.

Third, the MPEP acknowledges that **where, as here, "prior art compounds have no utility or utility only as intermediates, claimed structurally similar compounds may not be obvious over the prior art. MPEP 2144.09(VI). The sole utility which the '417 patent ascribes to the compounds pointed out by the Office as being allegedly similar to the compounds of the rejected claims is as intermediates in the synthesis of other compounds.**

The Federal Circuit has made it clear that the reason for modifying the prior art intermediate compound does not arise merely because the final product in the synthetic route has a disclosed utility. *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984). For example, in *Lalu*, the claimed compounds were structurally similar to prior art intermediate compounds used to form useful fluorinated sulfonic acids. *Id.* at 1257-58. The Federal Circuit overturned a finding of obviousness which was based on the structural similarity of the intermediate and claimed compounds, stating that a *prima facie* case of obviousness cannot be premised on mere structural similarity when there is no utility disclosed for the prior art compound, as was the case for the intermediates in *Lalu*. *Id.* at 1259-60. Further, the fact that the end products of the synthesis had utility was insufficient basis for a *prima facie* case of obviousness. *Id.* Instead, the court emphasized that there must be a reason to stop the synthesis at the intermediate stage, isolate the intermediate compound, and test it for certain properties with a reasonable expectation of producing an active compound:

> That there is no common-properties presumption accorded to an intermediate and the end product of the reaction involving that intermediate necessarily means that there is no presumption that an intermediate's utility would be the same as that of the end product....There is no disclosure that the Oesterling compounds would have any properties in common with those of appellants' compounds, as those properties of the former relate to the use of the compounds for base neutralization, catalysis, metal cleaning, and fuel. The mere fact that Oesterling's sulfonyl chlorides can be used as intermediates in the production of the corresponding sulfonic acids does not provide adequate motivation for one of ordinary skill in the art to stop the Oesterling synthesis and investigate the intermediate sulfonyl chlorides with an expectation of arriving at appellants' claimed sulfonyl halides for use as corrosion inhibiting agents, surface active agents, or leveling agents.
>
> *Id.*

Fourth, by pointing to the failure of claim 1 to exclude "ethyl or ethoxy versions" of 1-(4-methoxyphenyl)-2-methyl-piperazine as the sole reason for maintaining the rejection (or, at least, the only reason which is not inaccurate), it appears that the Office would hold any compound which is a homolog or positional isomer of a known compound obvious. The use of such a *per se* rule of prima facie obviousness is inappropriate and inconsistent with Federal Circuit specifically forbidding reliance on such rules. The *Grabiak*, the court stated that "generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other" and that "there must be adequate support in the prior art for the ... change in structure, in order to complete the PTO's prima facie case and shift the burden of going forward to the applicant." *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985). In *Deuel*, the court also rejected the application of a *per se* rule, stating that where "the prior art teaches a specific, structurally-definable compound and the question becomes *whether the prior art would have suggested making the specific molecular modifications necessary* to achieve the claimed invention." *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) (emphasis added). In Ochiai, the court was even more emphatic, stating that: "The use of per se rules...flouts section 103 and the fundamental case law applying it. [R]eliance on per se rules of obviousness is legally incorrect and must cease. [O]ur precedents do not establish any per se rules of obviousness"). *In re*

Ochiai, 71 F.3d. 1565, 1572 (Fed. Cir. 1995). The law, and the MPEP, do not sanction the use of such *per se* rules. The MPEP instead requires that the *Graham* standard be applied in "each and every case". MPEP 2141(I).

Finally, another point made previously by the applicants but disregarded by the Office in reconsidering the rejection over the '417 patent is that the rejection fails to take into account the useful biological activity of the presently claimed compounds, which is completely unexpected over the disclosure of the '417 patent (where the compounds that are supposedly structurally similar to the compounds of the present invention are only disclosed as synthetic intermediates). The MPEP reminds examiners that evidence of secondary considerations such as unexpected results must always be considered in determining whether an invention is obvious. Here, if the Examiner had established a *prima facie* case of obviousness by citing the '417 patent, any such case must be considered rebutted by the unexpected and useful biological activity exhibited by the presently claimed compounds described in the specification. Even if the '417 patent had, in some abstract sense, "suggested" compounds according to the rejected claims, the person skilled in the art clearly could not have expected the compounds to have useful biological activity as disclosed in the present application. The Examiner does not appear to have considered such unexpected results either when originally making the obviousness rejection. Neither is there any indication in the most recent Office Action that the unexpected results have been taken into account in reconsidering the obviousness rejection, despite the applicants having raised the issue in their response to the prior Office Action.

While the foregoing remarks apply to all the claims, the applicants respectfully point out that the rejection is also deficient in its reasoning as to how the elements of the dependent claims would have been suggested by the prior art reference. For example:

A compound having R_1 as C_{1-8} alkyl (claim 3), R_2 as C_{2-4} alkenyl (claim 9), R_3, R_4, R_5, R_6 and R_7 each independently selected from the group consisting of H, CH_3, CH_2CH_3, $CH(CH_3)_2$, cyano, OCF_3, CF_3, F, Cl and Br (claim 20) or H, CF_3, F, Cl and Br (claim 21) or a compound

according to claim 79 could not be an "ethyl version" "positional isomer" of 1-(4-methoxyphenyl)-2-methyl-piperazine.

No explanation is provided of how the'417 patent might suggest a compound wherein R_3, R_4, R_5, R_6 and R_7 are each independently selected from the group consisting of H, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and halogen (claim 19).

Based on the foregoing, since the Office has not established that the rejected claims would have been obvious over the '417 patent, reconsideration and withdrawal of the rejection of claims 1-2, 11-12, 17, 19-26, and 79 under 35 U.S.C. § 103(a) over the '417 patent is once again respectfully requested.

2. Rejection of Claims 1, 3, 11, 12, 17, 19-25 and 79 over Kametani *et al*, *J. Org. Chem.*, 1972, 35, 1450-53.

Claims 1, 3, 11, 12, 17, 19-25 and 79 were rejected under 35 U.S.C. § 103(a) over Kametani *et al*, *J. Org. Chem.*, **1972**, *35*, 1450-53 ("Kametani"). Applicants respectfully traverse the rejection.

The prior Office Action maintained that "[g]enerically, claim 1 [*sic*] of [Kametani] renders the scope of instant claim 1 obvious" and "2,4-dimethyl-1-phenylpiperazine" which was said to be disclosed in the reference "render[ed] claim 1 obvious". It was maintained that the compounds of the rejected claims would have been obvious because "one skilled in the art would have been motivated to prepare compounds as taught in the reference with the expectation of obtaining compounds falling within the generic teaching of claim 1 [*sic*]."

In response to the rejection, the applicants requested clarification of the Office's reference to "claim 1 of the reference" because it was not understood what "generic disclosure" of "claims" of the reference the Office Action was referring to. Although the Office did not provide any such explanation, the applicants note that the Office (without acknowledging the

applicants' observations) has dropped its assertion that Kametami has "claims" whose "generic disclosure" rendered the subject matter of the rejected claims of the obvious.

The applicants also pointed out that Kametami discloses 2,4-dimethyl-1-phenylpiperazine, a compound which is expressly excluded from the claims, only as a minor by-product (formed in 2.5% yield) from the reaction of bromobenzene with N,N'-dimethylpiperazine. The applicants pointed out that the reference's disclosure of 2,4-dimethyl-1-phenylpiperazine does not anticipate the rejected claims because the compound was expressly excluded from the scope of the rejected claims.

The applicants further pointed out that in order to maintain a rejection for obviousness, the Office must explain why it would have been obvious to modify the reference to make compounds within the scope of the claims. As the court held in *Takeda*, it is "necessary to identify some reason that would have led a chemist to modify a known compound *in a particular manner* to establish *prima facie* obviousness" and that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention' [is] also required." *Takeda*, 492 F.3d at 1356-57 (Fed. Cir. 2007) (quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)) (emphasis added).

In the most recent Office Action, the Office has continued in its failure to provide any reason as to why the Kametani reference would provided the person skilled in the art with a reason to modify a known compound in the "particular manner" that would be required to provide a compound within the scope of the claims. The only reasoning which the Office provides for maintaining the rejection is as follows:

> Although the proviso of claim 1 does in fact exclude the compound 2,4-dimethyl-l-phenyl-piperazine ... from claim 1, the proviso does not exclude the ethyl version of this exemplified compound, or positional isomers. As such. Examiner maintains this rejection of claims 1, 3, 11, 12, 17, 19-25 and 79.

It appears from what little reasoning the Office Action has provided that the Examiner considers that it would somehow have been obvious from the person skilled in the art at the time that the invention was made to make an "ethyl version" or positional isomer of 2,4-dimethyl-l-phenyl-piperazine within the scope of the claims.

The Office Action, however, does not identify any *reason* as to why it would have been obvious to the person skilled in the art to modify 2,4-dimethyl-l-phenyl-piperazine to make an "ethyl version" or "positional isomer" of that compound which is within the scope of the claims, even though such a reason would be essential to support an obviousness rejection. *KSR* requires an *explicit rationale* for why one having ordinary skill in the art would have modified the prior art in the manner claimed to be provided. *KSR,* 127 S.Ct. at 1741. *Takeda* explains that it is "necessary to identify some *reason* that would have led a chemist to modify a known compound *in a particular manner* to establish *prima facie* obviousness". *Takeda*, 492 F.3d at 1356-57 (Fed. Cir. 2007)

Kametani fails to disclose anything about 2,4-dimethyl-1-phenylpiperazine other than the fact that it can be isolated as a minor byproduct of a chemical reaction. **Neither the reaction itself nor 2,4-dimethyl-1-phenylpiperazine are disclosed by Kametani as having any utility whatsoever.**

The applicants respectfully submit there would have been no reason for the person skilled in the art to which the present invention pertains to modify Kametani to make compounds within the scope of the rejected claims.

First, Kametani is not analogous art relative to the present invention. In order to be relied upon to support a rejection under 35 U.S.C. §103(a), a reference must be analogous art, meaning that it is a reference which "because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his or her invention as a whole." MPEP 2141.01(a). The applicant's invention relates to the development of compounds for the modulation of $5HT_{2C}$ receptors. Kametani, on the other hand, is concerned with an abstract

studies of the chemical reactivity of the "Benzyne Reaction of Halogenobenzenes with N-Alkylmorpholines". Kametani reports no practical utility whatsoever of the reactions or the compounds described therein. There would be no reason that Kametani's description of reactions and compounds having no disclosed utility "would have commended itself" to the inventors' attention in considering their novel $5HT_{2C}$ receptor modulators.

Second, the MPEP acknowledges that **where, as here, "prior art compounds have no utility or utility only as intermediates, claimed structurally similar compounds may not be obvious over the prior art. MPEP 2144.09(VI).** Since **Kametani describes reactions and compounds having no disclosed utility**, the person skilled in the art would have no reason to modify Kametani the reactions described in Kametani to perform similar reactions on different substrates to provide an "ethyl version" or "positional isomer" of 2,4-dimethyl-l-phenyl-piperazine. The MPEP explains that any "obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." MPEP 2144.09 (citing *In re Payne*, 606 F.2d 303, 313 (CCPA 1979)). No such motivation would exist when a structurally similar compound in a reference has no useful properties. Indeed, the MPEP expressly acknowledges that **where "the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is unlikely to render structurally similar claims prima facie obvious in the absence of any reason for one of ordinary skill in the art to make the reference compounds or any structurally related compounds." MPEP 2144.09(VI)** (citing *In re Stemniski*, 444 F.2d 581 (CCPA 1971).

Third, by pointing to the failure of claim 1 to exclude an "ethyl version" or "positional isomer" of 2,4-dimethyl-l-phenyl-piperazine as the sole reason for maintaining the rejection it again appears that the Office would hold any compound which is a homolog or positional isomer of a known compound obvious. As the applicants have pointed out above, the use of such a *per se* rule of prima facie obviousness is inconsistent with Federal Circuit specifically forbidding reliance on such rules. The Office is directed to the applicants' discussion of *In re Grabiak*, 769

F.2d 729, 731 (Fed. Cir. 1985), *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) and *In re Ochiai*, 71 F.3d. 1565, 1572 (Fed. Cir. 1995) above. The law, and the MPEP, do not sanction the use of such *per se* rules, but instead the MPEP requires that the *Graham* standard be applied in "each and every case". MPEP 2141(I).

Fourth, the Office Action does not indicate how it would be obvious that an "ethyl version" or positional isomer of 2,4-dimethyl-l-phenyl-piperazine could even be made using the chemistry described by Kametani. The chemical reaction forming 2,4-dimethyl-l-phenyl-piperazine shown in Scheme I of Kametani. The reaction starts with a symmetrically disubstituted piperazine (1,4-dimethyl piperazine) and one of the N-substituent methyl groups of the piperazine migrates to position 2 as a result of a Stevens rearrangement, resulting in a very low yield (2.5%) of 2,4-dimethyl-l-phenyl-piperazine. It is not clear that regioisomers could be formed because the positions of the 2 and 4 methyl groups are fixed by the chemistry. It is also not clear that an ethyl group could be substituted for one (or both) of the methyl groups with the same result since Kametani does not show a Stevens migration involving an ethyl group.

Finally, the applicants point with regard to unexpected results made with regard to the rejection over the '417 patent is also applicable to the rejection over Kametani. Even if the Office were to hold that a prima facie case of obviousness over Kametani has been established, any such prima facie case must be considered to be overcome by the unexpected, useful biological activity shown by the presently claimed compounds. Kametani describes the once compound that the Office supposes is structurally similar to the compounds of the present invention only as a minor by-product (2.5% yield). No utility or biological activity of the compound is disclosed. The specification of the present application discloses the claimed compounds to be useful as 5-HT_{2C} modulators, which must be considered as unexpected in view of the lack of a disclosed utility in Kametani. The MPEP reminds examiners that evidence of secondary considerations such as unexpected results must always be considered in determining whether an invention is obvious. Here, if the Examiner had established a *prima facie* case of obviousness by citing the Kametani, any such case must be considered rebutted by the

unexpected and useful biological activity exhibited by the presently claimed compounds described in the specification. Even if Kametani had, in some abstract sense, "suggested" compounds according to the rejected claims, the person skilled in the art clearly could not have expected the compounds to have useful biological activity as disclosed in the present application. The Examiner does not appear to have considered such unexpected results when originally making or maintaining the obviousness rejection.

Based on the foregoing, since the Office has not established that the rejected claims are obvious over the Kametani, reconsideration and withdrawal of the rejection of claims 1, 3, 11, 12, 17, 19-25 and 79 is respectfully requested.

V. Response to the Rejection of Claims 1-2, 11-12, 17, 19-26, 32 and 79 under 35 U.S.C. § 102(a) over Allen, U.S. Patent No. 3,751,417.

Claims 1-2, 11-12, 17, 19-26, 32 and 79 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by Allen, U.S. Patent No. 3,751,417 (the "'417 patent"). The applicants respectfully traverse the rejection.

The Office asserts that the '417 patent discloses 2-methyl-l-(4-methylphenyl)-piperazine, and that this disclosure anticipates the rejected claims wherein R^2 and R^5 are C_1 alkyl, and R^1, R^3, R^4 and R^6 are all hydrogen.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)).

The applicants once again respectfully point out that 2-methyl-l-(4-methylphenyl)-piperazine is not within the scope of the rejected claims, and therefore each and every element of the claim is not found in the reference. Claim 1 includes a proviso which expressly excludes 2-methyl-l-(4-methylphenyl)-piperazine, which reads, in relevant part: "provided that the compound is not ... 2-Methyl-1-p-tolyl-piperazine." The applicants respectfully point out that

this proviso expressly excludes -methyl-l-(4-methylphenyl)-piperazine because the term "p-tolyl" refers a "4-methylphenyl" group, as evidenced by the definition from the *Shorter Oxford English Dictionary* (Oxford University Press, 6th Edition, 2007) reproduced below (the p-, an abbreviation for "para", referring to the methyl substituent being in the 4-position of the phenyl ring):

tolyl /'tɒlʌɪl, -ɪl/ *noun.* M19.
[ORIGIN from TOL(UENE + -YL.]
CHEMISTRY. Each of three isomeric cyclic radicals, $CH_3C_6H_4$·, derived from toluene. Formerly also = BENZYL.

Lest there be any doubt, the applicants expressly provided the structure of 2-methyl-1-p-tolyl-piperazine, the compound expressly excluded from the scope of claim 1 and all its dependent claims, in Table 3 on p. 43 of the specification. The compound in the third row of Table 3 on p. 43, identified as 2-methyl-1-p-tolyl-piperazine, the compound *expressly excluded* from claim 1, has **exactly the same structure** as the compound (2-methyl-1-(4-methylphenyl)-piperazine) in the reference which the Office Action contends anticipates the claim.

Since 2-methyl-l-(4-methylphenyl)-piperazine is expressly excluded from the scope of claim 1, the '417 patent's alleged disclosure of 2-methyl-l-(4-methylphenyl)-piperazine could not anticipate claim 1. Further, the '417 patent's alleged disclosure of 2-methyl-l-(4-methylphenyl)-piperazine also cannot anticipate any of claims 2, 11-12, 17, 19-26, 32 and 79 because these claims all depend from claim 1 and incorporate all its limitations, including the proviso excluding 2-methyl-l-(4-methylphenyl)-piperazine.

Based on the foregoing, the applicants respectfully request that the rejection claims 1-2, 11-12, 17, 19-26, 32 and 79 under 35 U.S.C. § 102(b) be withdrawn.

V. Conclusion

Based on the foregoing, it is respectfully submitted that the grounds of rejection have been overcome and that the application is in condition for allowance. An early action toward that end is therefore respectfully requested.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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